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Exhibit I

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Stereotactic Administration of Intratumoral Chronic Chemotherapy of Recurrent Malignant Gliomas

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Abstract. There is a continuous search for more efficient treatment of malignant cerebral gliomas. The work of Penn and Croin [9] demonstrates clearly that survival of rats having experimental gliomas is significantly increased by intratumoral chemotherapy. It has been shown that chronic depth electrodes for the investigation of epileptic patients is a reliable and safe method. Using this proven technology originally developed by Talairach, Szikla and co-workers we have developed catheters for intratumoral chemotherapy. Three patients have been treated. It is premature to pretend that this is a treatment which will lengthen the patient's life. Nevertheless, the feasibility of the technique, its precision and safety are assured. Following this course of treatment, we have seen no deteriorations, no side effects, no bone marrow depressions, and no sign of toxicity. Chemical analysis has shown that cisplatin was delivered to the tumor.

A cure for most malignant gliomas remains beyond reach. Very little progress has been made in the past 15 years. Perhaps the most important contribution has been radiosurgery, mainly interstitial irradiation of low grade gliomas, provided the tumor is less than 5 cm.

New therapeutic modalities are urgently needed, and, among these, chemotherapy appears to be a valuable tool. Many chemotherapeutic agents used to treat tumors in many parts of the body do not reach brain tissues because of the blood-brain barrier or because, as in the case of cisplatin, of the protein binding in the blood. To avoid systemic toxicity and achieve the greatest concentration of a drug into a tumor, many different chemotherapy approaches have been attempted.

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In 1973, Garfield and Dayan [6] reported the use of postoperative intracavitary chemotherapy of malignant gliomas. In 8 patients, high doses of methotrexate were injected through an indwelling catheter into the bed of the tumor after craniotomy. Accordingly to these authors, this technique appears to be a valuable adjunct to the treatment of cerebral tumors with cytotoxic drugs, since it does not necessitate exposure of other body tissues to chemotherapeutic agents.

In 1975, Garfield et al. [7] reported 10 patients with malignant astrocytomas treated with intracavitary injection of BCNU. The pathological findings were of acute necrosis in the wall of the cavity to a depth of 0.8–1.5 cm.

In 1980, Bosch et al. [2] proceeded to intraneoplastic administration of bleomycin in intracerebral gliomas.

Following a stereotactic biopsy using Leksell's technique, a small catheter was placed at the target by the same route and fixed to the skin with a suture. When the pathologists confirmed the diagnosis and described the glioma as malignant, introduction of bleomycin was begun. Five milligrams was dissolved in 5 ml of NaCl (0.9%) and injected by way of a syringe pump at a rate of 1 ml/h. The same procedure was repeated twice with 2 days' delay between the three administrations. One of these patients seemed to do very well with this treatment for a follow-up period of 2 years.

Blasberg et al. [1] used an intrathecal route and Dahhill et al. [5] did a prolonged and continuous intraventricular infusion of MTX. Their patients developed neurological toxicity. In 1984, Stewart [10] published an excellent review of intraarterial administration of chemotherapy. This method, as Stewart said, is worth pursuing because it offers at least the potential of achieving palliation.

The rationale presented by Kroin and Penn [8] and Penn et al. [9] is that chronic intratumoral microinfusion in rats can be used to produce adequate and sustained therapeutic drug levels over a considerable region of tissue without the problem of systemic toxicity. Injection of cisplatin and fluorouracil has produced statistically significant increases in survival, as compared to the control animals. They found that cisplatin does not diffuse more than 1 cm in rat brain tissue. This has stimulated us to find a new way for chronic microinfusion of chemotherapeutic agent on human gliomas using multiple sites of injection. Such an approach theoretically produces no exposure of other body tissues to the chemotherapeutic agent. Based on our experience with chronic

depth electrodes for epilepsy [9], we developed a similar technique for chronic intratumoral microinfusion of chemotherapeutic agent delivered throughout the tumor [3, 4].

Protocol

Patients admitted so far in our protocol have had all the accepted conventional therapy for malignant gliomas. Since they were showing signs of recurrence and nothing else could be done, we proposed stereotactic introduction of multiple catheters for chronic delivery of cisplatin as a last chance. All patients and their families knew that this was an experimental approach and that the results or complications were not known.

Method and Results

A catheter bundle consisting of four small catheters within an outer sheath was used to deliver drug into the brain. The outer diameter of the semiflexible vinyl sheath was 1.6 mm [10]. The first patient with 16 bundles (64 sites of injection) received 8.2 ml of cisplatin, whereas the other 2 patients received 12.5 ml at 100 sites of injection throughout the tumor. The concentration of cisplatin was 1 mg/ml. Once the volume of the lesion has been defined in three dimensions, the catheters are inserted with the Talairach stereotactic frame modified by us, and remain fixed to the bony anchor [9]. Three patients were treated with a survival of 6 months.

Discussion

Drug analyses were done by Stewart [10] and showed presence of cisplatin in the tumor. Histological study showed indirect signs of efficiency of the agent. Chronic intratumoral microinfusion is feasible and so far there is no mortality nor morbidity and no signs of toxicity. This technique offers the possibility of a greater period of time over which the tumor is exposed to the maximum concentration of a drug. Direct injection decreases systemic exposure to the drug and thereby decreases systemic toxicity. Direct infusion also permits the injection of a small dose of a highly concentrated drug. New imaging techniques will allow us to trace the drug into the tumor and help us to find if the drug

can effectively act on tumorous cells. As long as chemotherapy is accepted as a therapeutic tool for malignant gliomas, in situ injection seems to be the best method. We have not proven yet that intratumoral injection of drug is very effective, but we can say that it is a logical and feasible approach that deserves more trial.

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